

**AMENDMENTS TO THE CLAIMS**

1. (Currently amended) A method of measuring the amount of an unlabeled organic acid in a biological sample, comprising:

- a) adding to a biological sample suspected of containing the unlabeled organic acid to be measured an amount of a standard comprising one or more oxygen-18 labeled organic acids, wherein at least one of the oxygen-18 labeled organic acids belongs to an organic acid class selected from the group consisting of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, glyoxylic acid, hydroxyl mono-acid selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxy isovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaproic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, indoleacetic acid and 3-hydroxydodecanoic acid, and keto acid, and wherein at least one of said oxygen-18 labeled organic acids is structurally similar or identical to the unlabeled organic acid to be measured;
- b) processing the sample;
- c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample by mass spectrometry; and
- d) using the amount of oxygen-18 organic acid measured in step c) to adjust the amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.

2. (Canceled)

3. (Currently amended) The method of claim 2 claim 1, wherein said mass spectrometry is gas chromatography—mass spectrometry.

4. (Currently amended) The method of claim 2 claim 1, wherein said mass spectrometry is liquid chromatography—mass spectrometry.
5. (Cancelled).
6. (Original) The method of claim 1, wherein said sample is a urine sample.
7. (Original) The method of claim 1 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.
8. (Original) The method of claim 1, wherein said processing results in chemical modification of the unlabeled organic acid.
9. (Currently amended) A method of measuring the amount of at least one unlabeled organic acid in a biological sample, comprising;
  - a) adding to a biological sample suspected of containing the at least one unlabeled organic acid to be measured an amount of at least one oxygen-18 labeled organic acid acids, wherein the oxygen-18 labeled organic acids comprise at least one acid selected from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid;
  - b) processing the sample;
  - c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample by mass spectrometry; and
  - d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the amount of a structurally similar or identical unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample.
10. (Previously presented) The method of claim 9 wherein at least two oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid are added to said sample.

11. (Previously presented) The method of claim 9 wherein at least 3 or more oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid are added to said sample.

12. (Original) The method of claim 9 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.

13. (Original) The method of claim 9 wherein said processing results in chemical modification of the unlabeled organic acid.

14. (Cancelled)

15. (Original) The method of claim 9, wherein said mass spectrometry is gas chromatography—mass spectrometry.

16. (Original) The method of claim 9, wherein said mass spectrometry is liquid chromatography—mass spectrometry.

17. (Original) The method of claim 9, wherein said sample is a urine sample.

18.-29. (Cancelled).

30. (Currently amended) A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of an unlabeled organic acid in a biological sample of the individual, said method comprising:

a) adding to a biological sample from the individual an amount of a standard comprising one or more oxygen-18 labeled organic acids, wherein at least one of the oxygen-18 labeled organic acids belong to an organic acid class selected from the group consisting of dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, glyoxylic acid, hydroxyl mono-acid selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric

acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxy isovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaproic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, indoleacetic acid and 3-hydroxydodecanoic acid, and keto acid, and wherein at least one oxygen-18 labeled organic acid is structurally similar or identical to the unlabeled organic acid to be measured;

b) processing the sample;

c) measuring the amount of unlabeled organic acid and oxygen-18 organic acid in the processed sample by mass spectrometry;

d) using the amount of oxygen-18 organic acid measured in step c) to adjust the amount of unlabeled organic acid measured in the processed sample so as to reflect the amount of unlabeled organic acid originally present in the sample; and

e) determining if the amount of the unlabeled organic acid detected in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

31. (Original) The method of claim 30 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.

32. (Original) The method of claim 30 wherein said processing results in chemical modification of the unlabeled organic acid.

33. (Canceled)

34. (Currently amended) The method of ~~claim 33~~ claim 30, wherein said mass spectrometry is gas chromatography—mass spectrometry.

35. (Currently amended) The method of ~~claim 33~~ claim 30, wherein said mass spectrometry is liquid chromatography—mass spectrometry.

36. (Original) The method of claim 30 wherein said sample is a urine sample.

37. (Currently amended) A method of diagnosing an individual with a metabolic defect characterized by an abnormal amount of at least one unlabeled organic acid in a sample of the individual, said method comprising:

a) adding to a sample from the individual an amount of ~~at least one~~ oxygen-18 labeled organic acid acids, wherein ~~at least one~~ the oxygen-18 labeled organic acid is acids comprise at least one acid selected from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate, and keto acid;

b) processing the sample;

c) measuring the amount of unlabeled organic acids and oxygen-18 organic acids in the processed sample by mass spectrometry;

d) using the amount of an oxygen-18 organic acid measured in step c) to adjust the amount of a structurally similar or identical unlabeled organic acid measured in the processed sample so as to reflect the amount of the at least one unlabeled organic acid originally present in the sample; and

e) determining if the amount of the at least one unlabeled organic acid originally present in the sample is an abnormal amount, thereby diagnosing the existence a metabolic defect in the individual.

38. (Previously presented) The method of claim 37 wherein at least two oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid are added to said sample.

39. (Previously presented) The method of claim 37 wherein at least 3 or more oxygen-18 labeled organic acids from each of hydroxy mono-acid, dihydroxy mono-acid, dicarboxyl organic acid, hydroxyl dicarboxyl acid, tricarboxyl acid, glycine conjugate and keto acid are added to said sample.

40. (Original) The method of claim 37 wherein said processing results in an enrichment of the unlabeled organic acid in the sample.

41. (Original) The method of claim 37 wherein said processing results in chemical modification of the unlabeled organic acid.

42. (Canceled)

43. (Currently amended) The method of ~~claim 42~~ claim 37, wherein said mass spectrometry is gas chromatography—mass spectrometry.

44. (Currently amended) The method of ~~claim 42~~ claim 37, wherein said mass spectrometry is LC liquid chromatography-mass spectrometry.

45. (Original) The method of claim 37 wherein said sample is a urine sample.

46. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a dihydroxy mono-acid.

47. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a dicarboxyl organic acid.

48. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a hydroxyl dicarboxyl acid.

49. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a tricarboxyl acid.

50. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a glycine conjugate.

51. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a glyoxylic acid.

52. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a hydroxyl mono-acid selected from the group consisting of glycolic acid, lactic acid, 3-hydroxypropionic acid, 2-hydroxybutyric acid, 3-hydroxyisobutyric acid, 3-hydroxybutyric acid, 4-hydroxybutyric acid, 2-hydroxyisovaleric acid, 3-hydroxy-2-methylbutyric acid, 3-hydroxy isovaleric acid, 3-hydroxy-2-ethylpropionic acid, 3-hydroxyvaleric acid, 4-hydroxyisovaleric acid, 5-hydroxyhexanoic acid, 2-hydroxyisocaprylic acid, 2-hydroxy-3-methylvaleric acid, 5-hydroxyhexanoic acid, 3-hydroxy-2-methylvaleric acid, 2-hydroxyphenylacetic acid, 4-hydroxy phenylacetic acid, 4-hydroxycyclohexylacetic acid, phenyllactic acid, 4-hydroxyphenylpropionic acid, 5-hydroxyindoleacetic acid, indoleacetic acid and 3-hydroxydodecanoic acid.

53. (Previously presented) The method of claim 1, wherein said oxygen-18 labeled organic acid is a keto acid.

54. (Previously presented) The method of claim 1, wherein said standard comprises at least two oxygen-18 labeled organic acids selected from two different organic acid groups.

55. (Previously presented) The method of claim 1, wherein said standard comprises at least three oxygen-18 labeled organic acids selected from three different organic acid groups.

56. (Previously presented) The method of claim 1, wherein said standard comprises at least four oxygen-18 labeled organic acids selected from four different organic acid groups.

57. (New) The method of claim 9, wherein the sample is a biological sample.

58. (New) The method of claim 1, wherein the sample is acidic.

59. (New) The method of claim 9, wherein the sample is acidic.

60. (New) The method of claim 30, wherein the sample is acidic.

61. (New) The method of claim 37, wherein the sample is acidic.